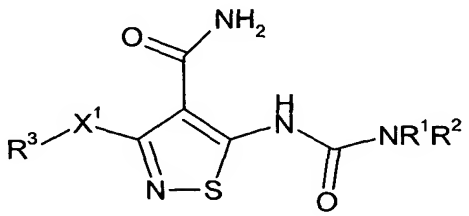
CLAIMS

1. A method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal in need of such treatment, either simultaneously or sequentially, (i) a therapeutically effective amount of a taxane derivative, a platinium coordination complex selected from the group consisting of carboplatin, tetraplatin, and topotecan, a nucleoside analog selected from the group consisting of gemcitabine hydrochloride and 5-FU, an anthracycline, a topoisomerase selected from the group consisting of etoposide, teniposide, amsacrine, topotecan, and Camptosar®, an aromatase inhibitor; and (ii) a therapeutically effective amount of a compound of the formula 1



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or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

wherein X^1 is O or S;

R^1 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -C(O)(C_1-C_{10} alkyl), -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(4-10 membered heterocyclic), -C(O)$(CH_2)_t$(C_6-C_{10} aryl), or -C(O)$(CH_2)_t$(5-10 membered heterocyclic), wherein t is an integer from 0 to 5; said alkyl group optionally includes 1 or 2 hetero moieties selected from O, S and -N(R^6)- with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; said aryl and heterocyclic R^1 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 5-10 membered heterocyclic group; 1 or 2 carbon atoms in the foregoing heterocyclic moieties are optionally substituted by an oxo (=O) moiety; the -$(CH_2)_t$- moieties of the foregoing R^1 groups optionally include a carbon-carbon double or triple bond where t is an integer from 2 to 5; and the foregoing R^1 groups, except H, are optionally substituted by 1 to 3 R^4 groups;

R^2 is selected from the list of substituents provided in the definition of R^1, -$SO_2(CH_2)_t$(C_6-C_{10} aryl), -$SO_2(CH_2)_t$(5-10 membered heterocyclic), and -OR^5, t is an integer ranging from 0 to 5, the -$(CH_2)_t$- moieties of the foregoing R^2 groups optionally include a carbon-carbon double or triple bond where t is an integer from 2 to 5, and the foregoing R^2 groups are optionally substituted by 1 to 3 R^4 groups;

or R^1 and R^2 may be taken together with the nitrogen to which each is attached to form a 4-10 membered saturated monocyclic or polycyclic ring or a 5-10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from O, S and -N(R^6)- in addition to the nitrogen to which R^1 and R^2 are attached,

said -N(R^6)- is optionally =N- or -N= where R^1 and R^2 are taken together as said heteroaryl group, said saturated ring optionally may be partially unsaturated by including 1 or 2 carbon-carbon double bonds, and said saturated and heteroaryl rings, including the R^6 group of said -N(R^6)-, are optionally substituted by 1 to 3 R^4 groups;

R^3 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -$(CH_2)_t$(C_6-C_{10} aryl), or -$(CH_2)_t$(5-10 membered heterocyclic), wherein t is an integer from 0 to 5; said alkyl group optionally includes 1 or 2 hetero moieties selected from O, S and -N(R^6)- with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; said aryl and heterocyclic R^3 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 5-10 membered heterocyclic group; 1 or 2 carbon atoms in the foregoing heterocyclic moieties are optionally substituted by an oxo (=O) moiety; the -$(CH_2)_t$- moieties of the foregoing R^3 groups optionally include a carbon-carbon double or triple bond where t is an integer from 2 to 5, and the foregoing R^3 groups are optionally substituted by 1 to 5 R^4 groups;

each R^4 is independently selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -OR^5, -$C(O)R^5$, -$C(O)OR^5$, -$NR^6C(O)OR^5$, -$OC(O)R^5$, -$NR^6SO_2R^5$, -$SO_2NR^5R^6$, -$NR^6C(O)R^5$, -$C(O)NR^5R^6$, -NR^5R^6, -$S(O)_jR^7$ wherein j is an integer ranging from 0 to 2, -SO_3H, -$NR^5(CR^6R^7)_tOR^6$, -$(CH_2)_t$(C_6-C_{10} aryl), -$SO_2(CH_2)_t$(C_6-C_{10} aryl), -$S(CH_2)_t$(C_6-C_{10} aryl), -$O(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5-10 membered heterocyclic), and -$(CR^6R^7)_mOR^6$, wherein m is an integer from 1 to 5 and t is an integer from 0 to 5; said alkyl group optionally contains 1 or 2 hetero moieties selected from O, S and -N(R^6)- with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; said aryl and heterocyclic R^4 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 5-10 membered heterocyclic group; 1 or 2 carbon atoms in the foregoing heterocyclic moieties are optionally substituted by an oxo (=O) moiety; and the alkyl, aryl and heterocyclic moieties of the foregoing R^4 groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -$NR^6SO_2R^5$, -$SO_2NR^5R^6$, -$C(O)R^5$, -$C(O)OR^5$, -$OC(O)R^5$, -$NR^6C(O)R^5$, -$C(O)NR^5R^6$, -NR^5R^6, -$(CR^6R^7)_mOR^6$ wherein m is an integer from 1 to 5, -OR^5 and the substituents listed in the definition of R^5;

each R^5 is independently selected from H, C_1-C_{10} alkyl, -$(CH_2)_t$(C_6-C_{10} aryl), and -$(CH_2)_t$(5-10 membered heterocyclic), wherein t is an integer from 0 to 5; said alkyl group optionally includes 1 or 2 hetero moieties selected from O, S and -N(R^6)- with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; said aryl and heterocyclic R^5 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 5-10 membered heterocyclic group; and the foregoing R^5 substituents, except H, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -$C(O)R^6$, -$C(O)OR^6$, -$CO(O)R^6$, -$NR^6C(O)R^7$, -$C(O)NR^6R^7$, -NR^6R^7, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy; and

each R^6 and R^7 is independently H or C_1-C_6 alkyl.

2. The method of claim 1, wherein the taxane is selected from the group consisting of paclitaxel and docetaxel.

3. The method of claim 2, wherein the taxane is paclitaxel.

4. The method of claim 2, wherein the taxane is docetaxel.

5. The method according to claim 1, wherein the nucleoside analog is gemcitabine hydrochloride.

6. The method according to claim 1, wherein the platinum coordination complex is selected from the group consisting of carboplatin and tetraplatin.

7. The method according to claim 6, wherein the platinum coordination complex is carboplatin.

8. The method according to claim 7, wherein the platinum coordination complex is tetraplatin.

9. The method according to claim 1, wherein the nucleoside analog is gemcitabine hydrochloride.

10. The method according to claim 1, wherein the nucleoside analog is 5-FU.

11. The method ccording to claim 1, wherein the anthracycline is selected from the group consisting of doxorubicin, carminomycin and aclacinomycin.

12. The method according to claim 10, wherein the anthracycline is doxorubicin.

13. The method according to claim 1, wherein the topisomerase is Camptosar®.

14. The method according to claim 1, wherein the aromatase inhibitor is selected from the group consisting of letrazole, vorazole, Aromasin® (exemestane), and anastrazole.

15. The method according to claim 14, wherein the aromatase inhibitor is selected from the group consisting of Aromasin® (exemestane), and anastrazole.

16. The method according to claim 15, wherein the aromatase inhibitor is Aromasin® (exemestane).

17. The method according to claim 15, wherein the aromatase inhibitor is anastrazole.

18. The method of claim 1, wherein the hyperproliferative disorder is cancer.

19. The method of claim 18, wherein said cancer is selected from the group consisting of brain, squamous cell, bladder, gastric, pancreatic, breast, head, neck, oesophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological and thyroid cancer.

20. The method of claim 19, wherein said cancer is selected from the group consisting of prostate, breast, lung, colon and ovarian cancer.

21. The method of claim 20, wherein said cancer is selected from the group consisting of prostate, breast, and lung cancer.

22. The method of claim 21, wherein said breast cancer is metastatic breast cancer.

23. The method of claim 21, wherein said lung cancer is non-small cell lung cancer.

24. The method of claim 1, wherein said hyperproliferative disorder is non-cancerous.

25. The method of claim 24, wherein non-cancerous hyperproliferative disorder is benign hyperplasia of the skin or prostate.

26. The method of claim 1, wherein said compounds (i) and (ii) are administered simultaneously.

27. The method of claim 1, wherein said compounds (i) and (ii) are administered sequentially.

28. The method of claim 1, wherein R^2 of the compound of formula 1 is H and R^1 is C_1-C_{10} alkyl optionally substituted by 1 or 2 substituents independently selected from $-NR^5R^6$, $-NR^5(CR^6R^7)_tOR^6$ and $-(CH_2)_t$(5-10 membered heterocyclic) wherein t is an integer from 0 to 5.

29. The method of claim 28, wherein R^1 of the compound of formula 1 is selected from propyl, butyl, pentyl and hexyl, and said R^1 groups are optionally substituted by dimethylamino, hydroxy, pyrrolidinyl, morpholino, and ethyl-(2-hydroxy-ethyl)-amino.

30. The method of claim 1, wherein R^2 of the compound of formula 1 is H and R^1 of the compound of formula 1 is $-(CH_2)_t$(5-10 membered heterocyclic), wherein t is an integer from 0 to 5; said heterocyclic group is optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 5-10 membered heterocyclic group; and said R^1 group, including the optionally fused portions of said R^1 group, is optionally substituted by 1 or 2 substituents independently selected from C_1-C_4 alkyl, hydroxy and hydroxymethyl.

31. The method of claim 30, wherein the heterocyclic moiety of said R^1 group is selected from morpholino, pyrrolidinyl, imidazolyl, piperazinyl, piperidinyl, and 2,5-diaza-bicyclo[2.2.1]hept-2-yl, the t variable of said R^1 group ranges from 2 to 5, and said R^1 group is optionally substituted by hydroxy, hydroxymethyl and methyl.

32. The method according to claim 1 wherein R^3 of the compound of formula 1 is $-(CH_2)_t$(C_6-C_{10} aryl) wherein t is an integer from 1 to 3 and said R^3 group is optionally substituted by 1 to 4 R^4 groups.

33. The method according to claim 32 wherein R^3 is benzyl optionally substituted by 1 to 4 substituents independently selected from halo and C_1-C_4 alkyl.

34. The method according to claim 33 wherein R^3 is benzyl substituted by 1 to 4 substituents independently selected from methyl, fluoro, chloro and bromo.

35. The method according to claim 1, wherein the compound of formula 1 is selected from the group consisting of

mesylate salt of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido}-isothiazole-4-carboxylic acid amide;

5-{3-[3-(4-Methyl-piperazin-1-yl)-propyl]-ureido}-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,6-difluoro-benzyloxy)-5-(3-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butyl}-ureido)-isothiazole-4-carboxylic acid amide;

3-(2-Fluoro-4-methyl-benzyloxy)-5-{3-[3-(4-methyl-piperazin-1-yl)-propyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(2,5-Difluoro-4-methyl-benzyloxy)-5-(3-4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-butyl}-ureido)-isothiazole-4-carboxylic acid amide;

3-(2,5-Difluoro-4-methyl-benzyloxy)-5-[3-(6-dimethylamino-hexyl)-ureido]-isothiazole-4-carboxylic acid amide;

3-(2-Fluoro-4-methyl-benzyloxy)-5-[3-(5-isopropylamino-pentyl)-ureido]-isothiazole-4-carboxylic acid amide;

hydrochloride salt of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido}-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,6-difluoro-benzyloxy)-5-{3-[3-(4-methyl-piperazin-1-yl)-propyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,6-difluoro-benzyloxy)-5-{3-[-(1-methyl-pyrrolidin-2-yl)-ethyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide;

3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-butyl}-ureido)-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,6-difluoro-benzyloxy)-5-[3-(3-hydroxy-5-pyrrolidin-1-yl)-pentyl)-ureido}-isothiazole-4-carboxylic acid amide;

3-(2,5-Difluoro-4-methyl-benzyloxy)-5-{3-[4-(3,4-dihydroxy-pyrrolidin-1-yl]-butyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,6-difluoro-benzyloxy)-5-{3-[4-(3,4-dihydroxy-pyrrolidin-1-yl)-butyl]-ureido}- isothiazole-4-carboxylic acid amide;

3-(2,5-Difluoro-4-methyl-benzyloxy)-5-{3-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-butyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,6-difluoro-benzyloxy)-5-{3-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-butyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(2,5-Difluoro-4-methyl-benzyloxy)-5-{3-[4-(3-hydroxy-pyrrolidin-1-yl)-butyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-(4-hydroxy-5-piperidin-1-yl-pentyl)-ureido]-isothiazole-4-carboxylic acid amide;

3-(2,5-Difluoro-4-methyl-benzyloxy)-5-{3-[4-(3-hydroxy-5-piperidin-1-yl-pentyl)-ureido]-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,6-difluoro-benzyloxy)-5-{3-[4-(2-hydroxymethyl-piperidin-1-yl)-butyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(2,5-Difluoro-4-methyl-benzyloxy)-5-(3-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butyl}-ureido)-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,6-difluoro-benzyloxy)-5-[3-(5-hydroxy-6-piperidin-1-yl)-hexyl)-ureido}-isothiazole-4-carboxylic acid amide;

3-(4-Bromo-2,3,6-trifluoro-benzyloxy)-5-{3-[3-(4-methyl-piperazin-1-yl)-propyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(2,6-Difluoro-4-methyl-benzyloxy)-5-{3-[3-(4-methyl-piperazin-1-yl-propyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-(3-hydroxy-5-pyrrolidin-1-yl-pentyl)-ureido]-isothiazole-4-carboxylic acid amide;

5-[3-(4-Pyrrolidin-1-yl-butyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

5-[3-(3-Hydroxy-5-pyrrolidin-1-yl-pentyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,6-difluoro-benzyloxy)-5-{3-[3-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-propyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-{3-[3-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-propyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-{3-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-{3-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-butyl]-ureido}-isothiazole-4-carboxylic acid amide;

5-{3-[2-(1-Methyl-pyrrolidin-2-yl)-ethyl]-ureido}-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

5-[3-(4-Dimethylamino-butyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

5-[3-(3-Dimethylamino-propyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

5-[3-(3-Hydroxy-5-isopropropylamino-pentyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

5-[3-(3-Isopropylamino-propyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

5-{3-[4-(4-Methyl-piperazin-1-yl)-butyl]-ureido}-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

5-(3-{4-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-butyl}-ureido)-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

5-[3-(3-Pyrrolidin-1-yl-propyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

5-[3-(4-Hydroxy-5-piperidin-1-yl-pentyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

3-(4Chloro-2,6-difluoro-benzyloxy)-5-[3-(4-imidazol-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide;

5-(3-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butyl}-ureido)-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-(2,3,6-trifluoro-benzyloxy)-5-{3-[4-(2-hydroxmethyl-piperidin-1-yl)-butyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-[3-(3-hydroxy-5-pyrrolidin-1-yl-pentyl)-ureido]-isothiazole-4-carboxylic acid amide;

3-(4-Bromo-2,6-difluoro-benzyloxy)-5-{3-[3-(4-methyl-piperazin-1-yl)-propyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(2,6-Difluoro-4-methyl-benzyloxy)-5-{3-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-(4-dimethylamino-butyl)-ureido}-isothiazole-4-carboxylic acid amide;

3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-(3-dimethylamino-propyl)-ureido]-isothiazole-4-carboxylic acid amide;

3-(4-Bromo-2,3,6-trifluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-[3-(4-imidazol-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,3,6-difluoro-benzyloxy)-5-(3-{3-[ethyl-(2-hydroxy-ethyl)-amino]-propyl}-ureido)-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,3,6-trifluoro-benzyloxy)-5-(3-{3-[ethyl-(2-hydroxy-ethyl)-amino]-propyl}-ureido)-isothiazole-4-carboxylic acid amide;

5-[3-(3-Methylamino-propyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

5-[3-(3-Amino-propyl)-3-methyl-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

5-[3-(4-Diethylamino-butyl)-ureido]-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

3-(2,6-Difluoro-4-methyl-benzyloxy)-5-[3-(3-pyrrolidin-1-yl-propyl)-ureido]-isothiazole-4-carboxylic acid amide;

3-(3-Chloro-2,6-difluoro-4-methyl-benzyloxy)-5-[3-(4-dimethylamino-butyl)-ureido]-isothiazole-4-carboxylic acid amide;

5-(3-{4-[Bis-(2-hydroxy-ethyl)-amino]-butyl}-ureido)-3-(2,6-difluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

and the pharmaceutically acceptable salts, prodrugs and solvates of said compounds.

36. The method according to claim 35, wherein the compound of formula 1 is selected from the group consisting of:

3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide

mesylate salt of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido}-isothiazole-4-carboxylic acid amide;

5-{3-[3-(4-Methyl-piperazin-1-yl)-propyl]-ureido}-3-(2,3,6-trifluoro-4-methyl-benzyloxy)-isothiazole-4-carboxylic acid amide;

3-(4-Chloro-2,6-difluoro-benzyloxy)-5-(3-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butyl}-ureido)-isothiazole-4-carboxylic acid amide;

3-(2-Fluoro-4-methyl-benzyloxy)-5-{3-[3-(4-methyl-piperazin-1-yl)-propyl]-ureido}-isothiazole-4-carboxylic acid amide;

3-(2,5-Difluoro-4-methyl-benzyloxy)-5-(3-4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-butyl}-ureido)-isothiazole-4-carboxylic acid amide;

3-(2,5-Difluoro-4-methyl-benzyloxy)-5-[3-(6-dimethylamino-hexyl)-ureido]-isothiazole-4-carboxylic acid amide;

3-(2-Fluoro-4-methyl-benzyloxy)-5-[3-(5-isopropylamino-pentyl)-ureido]-isothiazole-4-carboxylic acid amide;

hydrochloride salt of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido}-isothiazole-4-carboxylic acid amide;

and the pharmaceutically acceptable salts, prodrugs and solvates of said compounds.

37. The method according to claim 36, wherein the compound of formula 1 is selected from the group consisting of

3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide

mesylate salt of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido}-isothiazole-4-carboxylic acid amide;

hydrochloride salt of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido}-isothiazole-4-carboxylic acid amide;

and the pharmaceutically acceptable salts, prodrugs and solvates of said compounds.

38. The method according to claim 37, wherein the compound of formula 1 is hydrochloride salt of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido}-

isothiazole-4-carboxylic acid amide; and the pharmaceutically acceptable salts, prodrugs and solvates of said compound.

39. The method of claim 38, comprising a therapeutically effective amount of paclitaxel.

40. The method of claim 38, comprising a therapeutically effective amount of gemcitabine hydrochloride.

41. The method of claim 38, comprising a therapeutically effective amount of carboplatin.

42. The method of claim 38, comprising a therapeutically effective amount of gemcitabine hydrochloride.

43. The method of claim 38, comprising a therapeutically effective amount of doxorubicin.

44. The method according to claim 38, comprising a therapeutically effective amount of Camptosar®.

45. The method according to claim 38, comprising a therapeutically effective amount of Aromasin® (exemestane).

46. The method according to claim 38, comprising a therapeutically effective amount of anastrazole.

47. A pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises (i) a therapeutically effective amount of a taxane derivative, a platinium coordination complex selected from the group consisting of carboplatin, tetraplatin, and topotecan, a nucleoside analog selected from the group consisting of gemcitabine hydrochloride and 5-FU, an anthracycline, a topoisomerase selected from the group consisting of etoposide, teniposide, amsacrine, topotecan, and Camptosar®, an aromatase inhibitor; and (ii) a therapeutically effective amount of a compound of the formula 1, in combination with one or more pharmaceutically acceptable carriers or vehicles.

48. The pharmaceutical composition of claim 47, wherein the taxane is selected from the group consisting of paclitaxel and docetaxel.

49. The pharmaceutical composition of claim 48, wherein the taxane is paclitaxel.

50. The pharmaceutical composition of claim 48, wherein the taxane is docetaxel.

51. The pharmaceutical composition of claim 47, wherein the nucleoside analog is gemcitabine hydrochloride.

52. The pharmaceutical composition of claim 47, wherein the platinum coordination complex is selected from the group consisting of carboplatin and tetraplatin.

53. The pharmaceutical composition of claim 52, wherein the platinum coordination complex is carboplatin.

54. The pharmaceutical composition of claim 53, wherein the platinum coordination complex is tetraplatin.

55. The pharmaceutical composition of claim 47, wherein the nucleoside analog is gemcitabine hydrochloride.

56. The pharmaceutical composition of claim 47, wherein the anthracycline is selected from the group consisting of doxorubicin, carminomycin and aclacinomycin.

57. The pharmaceutical composition of claim 47, wherein the anthracycline is doxorubicin.

58. The pharmaceutical composition of claim 47, wherein the topisomerase inhibitor is selected from the group consisting of teniposide, amsacrine, topotecan, and Camptosar®.

59. The pharmaceutical composition of claim 58, wherein the topisomerase is Camptosar®.

60. The pharmaceutical composition of claim 47, wherein the aromatase inhibitor is selected from the group consisting of letrazole, vorazole, Aromasin® (exemestane), and anastrazole.

61. The pharmaceutical composition of claim 60, wherein the aromatase inhibitor is selected from the group consisting of Aromasin® (exemestane), and anastrazole.

62. The pharmaceutical composition of claim 61, wherein the aromatase inhibitor is Aromasin® (exemestane).

63. The pharmaceutical composition of claim 62, wherein the aromatase inhibitor is anastrazole.

64. A kit comprising in a first compartment a compound of formula 1 and in a second compartment a taxane derivative, a platinium coordination complex selected from the group consisting of carboplatin, tetraplatin, and topotecan, a nucleoside analog selected from the group consisting of gemcitabine hydrochloride and 5-FU, an anthracycline, a topoisomerase selected from the group consisting of etoposide, teniposide, amsacrine, topotecan, and Camptosar® or an aromatase inhibitor.

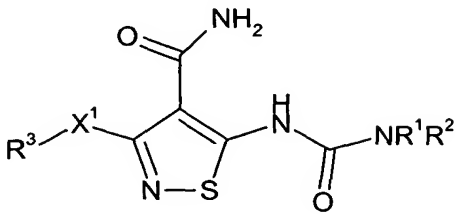
65. The kit of claim 64, whererin the compound in the second compartment is paclitaxel.

66. The kit of claim 64, whererin the compound in the second compartment is gemcitabine hydrochloride.

67. A method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal in need of such treatment, either simultaneously or sequentially, (i) a therapeutically effective amount of a taxane derivative, a platinium coordination complex selected from the group consisting of carboplatin, tetraplatin, and topotecan, a nucleoside analog selected from the group consisting of gemcitabine hydrochloride and 5-FU, an anthracycline, a topoisomerase selected from the group consisting of etoposide, teniposide, amsacrine, topotecan, and Camptosar®, an aromatase inhibitor; and (ii) a therapeutically effective amount of the hydrochloride salt of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido}-isothiazole-4-carboxylic acid amide.

68. A method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal in need of such treatment, either simultaneously or sequentially, (i) a therapeutically effective amount of a taxane derivative, a platinium coordination complex selected from the group consisting of carboplatin, tetraplatin, and topotecan, a nucleoside analog selected from the group consisting of gemcitabine hydrochloride and 5-FU, an anthracycline, a topoisomerase selected from the group consisting of etoposide, teniposide, amsacrine,

topotecan, and Camptosar®, an aromatase inhibitor; and (ii) a therapeutically effective amount of a compound of the formula 1



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or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

wherein X^1 is O or S;

R^1 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -C(O)(C_1-C_{10} alkyl), -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(4-10 membered heterocyclic), -C(O)$(CH_2)_t$(C_6-C_{10} aryl), or -C(O)$(CH_2)_t$(5-10 membered heterocyclic), wherein t is an integer from 0 to 5; said alkyl group optionally includes 1 or 2 hetero moieties selected from O, S and -N(R^6)- with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; said aryl and heterocyclic R^1 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 5-10 membered heterocyclic group; 1 or 2 carbon atoms in the foregoing heterocyclic moieties are optionally substituted by an oxo (=O) moiety; the -$(CH_2)_t$- moieties of the foregoing R^1 groups optionally include a carbon-carbon double or triple bond where t is an integer from 2 to 5; and the foregoing R^1 groups, except H, are optionally substituted by 1 to 3 R^4 groups;

R^2 is selected from the list of substituents provided in the definition of R^1, -$SO_2(CH_2)_t$(C_6-C_{10} aryl), -$SO_2(CH_2)_t$(5-10 membered heterocyclic), and -OR^5, t is an integer ranging from 0 to 5, the -$(CH_2)_t$- moieties of the foregoing R^2 groups optionally include a carbon-carbon double or triple bond where t is an integer from 2 to 5, and the foregoing R^2 groups are optionally substituted by 1 to 3 R^4 groups;

or R^1 and R^2 may be taken together with the nitrogen to which each is attached to form a 4-10 membered saturated monocyclic or polycyclic ring or a 5-10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from O, S and -N(R^6)- in addition to the nitrogen to which R^1 and R^2 are attached, said -N(R^6)- is optionally =N- or -N= where R^1 and R^2 are taken together as said heteroaryl group, said saturated ring optionally may be partially unsaturated by including 1 or 2 carbon-carbon double bonds, and said saturated and heteroaryl rings, including the R^6 group of said -N(R^6)-, are optionally substituted by 1 to 3 R^4 groups;

R^3 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -$(CH_2)_t$(C_6-C_{10} aryl), or -$(CH_2)_t$(5-10 membered heterocyclic), wherein t is an integer from 0 to 5; said alkyl group optionally includes 1 or 2 hetero moieties selected from O, S and -N(R^6)- with the proviso that two O

atoms, two S atoms, or an O and S atom are not attached directly to each other; said aryl and heterocyclic R^3 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 5-10 membered heterocyclic group; 1 or 2 carbon atoms in the foregoing heterocyclic moieties are optionally substituted by an oxo (=O) moiety; the $-(CH_2)_t-$ moieties of the foregoing R^3 groups optionally include a carbon-carbon double or triple bond where t is an integer from 2 to 5, and the foregoing R^3 groups are optionally substituted by 1 to 5 R^4 groups;

each R^4 is independently selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, $-NR^6C(O)OR^5$, $-OC(O)R^5$, $-NR^6SO_2R^5$, $-SO_2NR^5R^6$, $-NR^6C(O)R^5$, $-C(O)NR^5R^6$, $-NR^5R^6$, $-S(O)_jR^7$ wherein j is an integer ranging from 0 to 2, $-SO_3H$, $-NR^5(CR^6R^7)_tOR^6$, $-(CH_2)_t(C_6$-C_{10} aryl), $-SO_2(CH_2)_t(C_6$-C_{10} aryl), $-S(CH_2)_t(C_6$-C_{10} aryl), $-O(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5-10 membered heterocyclic), and $-(CR^6R^7)_mOR^6$, wherein m is an integer from 1 to 5 and t is an integer from 0 to 5; said alkyl group optionally contains 1 or 2 hetero moieties selected from O, S and $-N(R^6)-$ with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; said aryl and heterocyclic R^4 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 5-10 membered heterocyclic group; 1 or 2 carbon atoms in the foregoing heterocyclic moieties are optionally substituted by an oxo (=O) moiety; and the alkyl, aryl and heterocyclic moieties of the foregoing R^4 groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^6SO_2R^5$, $-SO_2NR^5R^6$, $-C(O)R^5$, $-C(O)OR^5$, $-OC(O)R^5$, $-NR^6C(O)R^5$, $-C(O)NR^5R^6$, $-NR^5R^6$, $-(CR^6R^7)_mOR^6$ wherein m is an integer from 1 to 5, $-OR^5$ and the substituents listed in the definition of R^5;

each R^5 is independently selected from H, C_1-C_{10} alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), and $-(CH_2)_t$(5-10 membered heterocyclic), wherein t is an integer from 0 to 5; said alkyl group optionally includes 1 or 2 hetero moieties selected from O, S and $-N(R^6)-$ with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; said aryl and heterocyclic R^5 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 5-10 membered heterocyclic group; and the foregoing R^5 substituents, except H, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^6$, $-C(O)OR^6$, $-CO(O)R^6$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy; and

each R^6 and R^7 is independently H or C_1-C_6 alkyl; and (iii) a therapeutically effective amount of an anti-hypertensive agent.

69. The method of claim 68, wherein the taxane is selected from the group consisting of paclitaxel and docetaxel.

70. The method of claim 69, wherein the taxane is paclitaxel.

71. The method of claim 69, wherein the taxane is docetaxel.

72. The method according to claim 68, wherein the nucleoside analog is gemcitabine hydrochloride.

73. The method according to claim 68, wherein the platinum coordination complex is selected from the group consisting of carboplatin and tetraplatin.

74. The method according to claim 73, wherein the platinum coordination complex is carboplatin.

75. The method according to claim 74, wherein the platinum coordination complex is tetraplatin.

76. The method according to claim 68, wherein the nucleoside analog is gemcitabine hydrochloride.

77. The method according to claim 68, wherein the anthracycline is selected from the group consisting of doxorubicin, carminomycin and aclacinomycin.

78. The method according to claim 68, wherein the topisomerase inhibitor is selected from the group consisting of teniposide, amsacrine, topotecan, and Camptosar®.

79. The method according to claim 78, wherein the topisomerase is Camptosar®.

80. The method according to claim 68, wherein the aromatase inhibitor is selected from the group consisting of letrazole, vorazole, Aromasin® (exemestane), and anastrazole.

81. The method according to claim 80, wherein the aromatase inhibitor is selected from the group consisting of Aromasin® (exemestane), and anastrazole.

82. The method according to claim 81 wherein the aromatase inhibitor is Aromasin® (exemestane).

83. The method according to claim 82, wherein the aromatase inhibitor is anastrazole.

84. The method according to claim 68, wherein the anti-hypertensive agent is selected from the group consisting of calcium channel blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (A-II antagonists), diuretics, beta-adrenergic receptor blockers (β-blockers), vasodilators and alpha-adrenergic receptor blockers (α-blockers).

85. The method according to claim 84, wherein the anti-hypertensive agent is an angiotensin converting enzyme inhibitors (ACE inhibitors).

86. The method according to claim 85, wherein the ACE inhibitor is accupril (quinapril) or accuretic (quinapril with hydrochlorothiazide).

87. The method according to claim 84, wherein the anti-hypertensive agent is an alpha-adrenergic receptor blocker (α-blocker).

88. The method according to claim 87, wherein the alpha-adrenergic receptor blocker (α-blocker) is selected from the group consisting of cardura (doxazosin) or cardura XL (doxazosin GITS).

89. The method according to claim 84, wherein the anti-hypertensive agent is a calcium channel blocker.

90. The method according to claim 89, wherein the calcium channel blocker is selected from the group consisting of Norvasc (amlodipine), procardia (nifedipine) and procardia XL (nifedipine GITS).

91. A method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal in need of such treatment, either simultaneously or sequentially: (i) a therapeutically effective amount of a taxane derivative, a platinium coordination complex selected from the group consisting of carboplatin, tetraplatin, and topotecan, a nucleoside analog selected from the group consisting of gemcitabine hydrochloride and 5-FU, an anthracycline, a topoisomerase selected from the group consisting of etoposide, teniposide, amsacrine, topotecan, and Camptosar®, an aromatase inhibitor; and (ii) a therapeutically effective amount of the hydrochloride salt of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido}-isothiazole-4-carboxylic acid amide; and (iii) a therapeutically effective amount an anti-hypertensive agent.

92. The method according to claim 91, wherein the anti-hypertensive agent is selected from the group consisting of calcium channel blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (A-II antagonists), diuretics, beta-adrenergic receptor blockers (β-blockers), vasodilators and alpha-adrenergic receptor blockers (α-blockers).